

REMARKS

Claims 1-22 were in the application as originally filed. Claims 5 and 10 were cancelled and claims 23-34 were added in the Preliminary Amendment filed on December 20, 2001. Claim 2 was cancelled in the amendment filed on April 22, 2004.

Claims 24 and 34 are withdrawn from consideration as being drawn to non-elected subject matter. Applicants reserve the right to pursue the subject matter of claims 24 and 34 in the pending or a subsequently filed continuing application.

New claim 35 is directed to subject matter cancelled from original claim 16 in the Preliminary Amendment. Claims 19-22 have been amended to change their dependency from claim 16 to new claim 35. Support for these amendments can be found, for example, in original claim 16.

Claim 7 has been amended in order to correct the obvious typographical errors in the words "diltazem," "gallopmil," "terbulaline," and "tamulosin" which now correctly read respectively as "diltiazem," "gallopamil," "terbutaline," and "tamsulosin." Support for these amendments can be found, for example, on page 5, lines 19-28 of the specification.

No new matter has been added by these amendments.

Claims 1, 3, 4, 7-9, and 11-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,834,024 issued to Heinicke et al. in view of U.S. Patent No. 5,725,883 issued to Staniforth et al., on the basis that Heinicke et al. allegedly disclose a diltiazem tablet formulation that comprises a core comprising diltiazem, a binder, emulsifier or stabilizer, and may further include a dispersing agent, glidant or surfactant, and the core can be coated with EUDRAGIT RL and EUDRAGIT RS. Staniforth et al. (U.S. Patent No. 5,725,883) is relied upon for an alleged disclosure of a pharmaceutical composition comprising active agents such as diltiazem, cationic surfactant such as benzalkonium chloride, and microcrystalline cellulose. The Examiner further maintains that a skilled artisan would incorporate an "amount of surfactant necessary as surface active agents" and concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the formulation of Heinicke and to use a benzalkonium chloride cationic surfactant with diltiazem according to Staniforth with expectation of a controlled release dosage form.

This rejection is traversed and reconsideration and withdrawal thereof are respectfully requested for the reasons given hereinbelow.

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The present invention generally provides controlled release dosage forms for pharmaceutical substances that *produce a timed pulse release*. The instant claims are specifically directed to delayed release coated cores containing an active substance with a polymer coating comprising an ammonio methacrylate copolymer. Additionally, the coated cores of the instant invention *must contain a cationic or zwitterionic* surfactant in an amount of from 10% to 50% relative to the amount of ammonio methacrylate copolymer in the coating.

The primary reference cited by the Examiner, Heinicke et al., discloses controlled absorption diltiazem pellets having a core containing diltiazem and a single layer coating. The coating contains a relatively large proportion of lubricant and a relatively small proportion of wetting agent in admixture with a minor proportion of a pharmaceutically acceptable film-forming polymer that is permeable to water and diltiazem and a second polymer that is less permeable to water and diltiazem. Heinicke discloses EUDRAGIT RS and EUDRAGIT RL as possible "less permeable" polymers, and that the cores *may* include further components such as a dispersing agent, glidant, and/or surfactant. However, as the Examiner has acknowledged, the cited reference fails to describe the use of *any* cationic or zwitterionic surfactants, as required by the instant invention. Furthermore, Heinicke et al. clearly do not suggest that such a surfactant might be used for diffusing into the polymer coating and at a given level provoking a sudden change in the coating's properties, as applicants have *surprisingly* found (Specification, page 3, lines 18-22 and page 4, lines 27-28). Thus, it is submitted that the primary Heinicke et al. reference is inadequate to either teach or suggest applicants' instantly claimed invention and, as pointed out hereinbelow, the secondary Staniforth et al. reference which is cited by the Examiner fails to cure the inadequacy of the primary reference.

The secondary reference cited by the Examiner, Staniforth et al., describes an excipient composition comprising a particulate agglomerate of co-processed microcrystalline cellulose and a surfactant, preferably an *anionic* surfactant, which are in intimate association with each other. Staniforth et al. describe numerous surfactants that may be used, including anionic surfactants, for example those containing carboxylate, sulfonate, and sulfate ions, for example sodium lauryl sulfate; alternative anionic surfactants including docusate salts, alkyl carboxylates, acyl lactylates, alkyl ether carboxylates, N-acyl sarcosinates, polyvalent alkyl carbonates, N-acyl glutamates, fatty acid, polypeptide condensates, and sulfuric acid esters; non-ionic surfactants including polyoxyethylene compounds, lecithin, ethoxylated alcohols, ethoxylated esters, ethoxylated amides, polyoxypropylene compounds, propoxylated alcohols, ethoxylated/propoxylated block polymers, propoxylated esters, alkanolamides, amine oxides, fatty acid esters of polyhydric alcohols, ethylene glycol esters,

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diethylene glycol esters, propylene glycol esters, glycerol esters, polyglycerol fatty acid esters, SPAN's, TWEEN's, glucose esters and simethicone; other pharmaceutically-acceptable surfactants including acacia, benzalkonium chloride, cholesterol, emulsifying wax, glycerol monostearate, lanolin alcohols, lecithin, poloxamer, polyethylene, and castor oil derivatives.

However, *none* of the actual examples provided by Staniforth et al. describes compositions utilizing *any* cationic or zwitterionic surfactant. Not only are anionic surfactants preferred, but each of Staniforth's examples using non-anionic surfactants produced less desirable results, thus *teaching away* from using non-anionic surfactants. It is only in hindsight view of the instant specification that one would pick and chose from the list of numerous surfactants disclosed in the cited patent a clearly non-preferred cationic or zwitterionic surfactant as required in the instant invention.

With respect to the amount of surfactant utilized, Staniforth et al. teach that the amount is generally "an effective amount, i.e. an amount which enhances or augments the compressibility of the microcrystalline cellulose" (column 5). The referenced patent does not teach using an "amount of surfactant necessary as surface active agent," as suggested by the Examiner. Moreover, the Examiner has failed to point to any evidence that the instantly claimed amount of cationic or zwitterionic surfactant would equate to an "amount of surfactant necessary as surface active agent," which amount the Examiner contends would be obvious to one skilled in the art. Staniforth et al., however, do teach that the range of the preferred surfactant, sodium lauryl sulfate, an anionic surfactant, is present in an amount of from about 0.1% to about 0.5% by weight of the microcrystalline cellulose, whereas the instant invention requires a cationic or zwitterionic surfactant in an amount of from 10% to 50% relative to the amount of ammonio methacrylate copolymer in the coating. Nowhere do Staniforth et al. teach or suggest the possibility or desirability of generating a delayed release coated core which produces a time-pulse release, and, therefore, the cited reference could not possibly suggest that modifying the amount of surfactant to the extent required by the instant invention would allow such a timed-pulse.

The Examiner must show that some teaching in the applied art or knowledge generally available would have led one skilled in the art to combine the cited references to arrive at the claim invention. As there is no specific teaching in either of the cited references with respect for the need for time-pulse controlled release formulations, the references can not be said to provide any motivation to the person of ordinary skill to pick and choose among the many disclosed excipients to arrive at the compositions and tablets of applicants' claims. Moreover, the Examiner has pointed to nothing in Staniforth that would even suggest what effect a cationic or zwitterionic

surfactant might have on the properties of the Heinicke compositions. In sum, the Staniforth disclosure fails to provide the requisite motivation to one of skill in the art to pick and choose among the numerous surfactants described so as to arrive at those of the instant invention, then to change the amount of surfactant present in the composition, and finally to combine such a surfactant with the compositions of Heinicke et al.

Accordingly, applicants submit that neither the primary Heinicke et al., reference nor the secondary Staniforth et al. reference taken alone or in combination are competent to render applicants' claimed invention obvious. The claimed invention would, therefore, not have been obvious to such a person at the time the invention was made and, hence, the rejection of claims 1, 3, 4, 7-9, and 11-15 under 35 U.S.C. § 103(a), based on said references is believed to be unwarranted and should be withdrawn.

Claims 1, 3, 4, 6-9, 11-23, and 25-33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wilson et al. (US 6,403,597) on the grounds that Wilson allegedly discloses a formulation that comprises active agent, sustained release carrier, phosphodiesterase, surfactant and excipients.

This rejection is traversed and withdrawal and reconsideration thereof are respectfully requested for the reasons given hereinbelow.

Initially, it is noted that the Wilson et al. reference (U.S. Patent 6,403,597) issued June 11, 2002, which date is after applicants' claimed foreign priority date of June 28, 1999, and international filing date of June 27, 2000. Therefore, the Wilson reference is not available as a reference under 35 U.S.C. § 102(a)/103 or 35 U.S.C. § 102(b)/103 against the instantly claimed invention. Moreover, Wilson et al. has a filing date of June 21, 2001, and, thus, it is unavailable as a prior art reference under 35 U.S.C. § 102(e)/103.

Inasmuch as the instant rejection is based on an earlier effective filing date for an application to which Wilson claims priority, the portions of Wilson relied upon for this rejection must necessarily be found in the disclosure of the previously filed application (e.g. U.S Patent No. 6,037,346, issued to Doherty et al., filed on February October 27, 1998) for Wilson to be available as prior art under 35 U.S.C. § 102(e)/103. Applicants respectfully submit that various portions of Wilson et al. principally relied upon by the Examiner for the instant rejection are not disclosed in Doherty et al., U.S. Patent No. 6,037,346. Specifically, the Examiner relies upon Wilson for the alleged disclosure of compositions containing EUDRAGIT RS sustained release carrier. The

Doherty patent on the other hand, describes formulations for *local administration* of phosphodiesterase inhibitors. In fact, the Doherty reference fails to disclose EUDRAGIT polymers or any other ammonio methacrylate copolymers, and, moreover, fails to describe a core of active substance coated with a polymer comprising an ammonio methacrylate copolymer, as required by applicants' invention. Thus, as the Doherty reference fails to teach or suggest applicants' claimed invention and, moreover, fails to disclose portions of Wilson relied upon by the Examiner for the instant rejection, the Doherty patent is irrelevant to the rejection at bar. Therefore, the Wilson reference is not available as prior art under 35 U.S.C. § 102(e)/103 against the instant invention.

Since the Wilson reference is not available as a reference under 35 U.S.C. § 102(a)/103, 35 U.S.C. § 102(b)/103, or 35 U.S.C. § 102(e)/103 against the instantly claimed invention, the rejection under 35 U.S.C. § 103(a) based on Wilson et al. is unwarranted and should therefore be withdrawn.

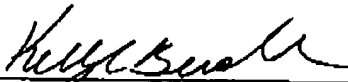
Applicants acknowledge the Examiner's indication that "[t]he prior art made of record and not relied upon is considered pertinent to applicant's disclosure...Mughal et al. (US 4,524,060)...and Staniforth (US 5,858,412) are equal importance as the references cited above" (March 9, 2005 Office Action, paragraph 6).

The Examiner has not used these references as a basis for any rejection. Accordingly, it is impossible for applicants to address these references.

There being no remaining issues, this application is believed in condition for favorable reconsideration and early allowance, and such actions are earnestly solicited.

The Commissioner is hereby authorized to charge any additional fees which may be required by this paper, or credit any overpayment to Deposit Account No. 18-1982.

Respectfully submitted,



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